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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,538	03/26/2001	Zuomei Li	106101.144	6847

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EXAMINER
EPPS FORD, JANET L

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 04/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,538	LI ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 June 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. The allowability of claim 7 set forth in the prior Office Action is withdrawn in view of the following grounds of rejection.

Drawings

3. The drawings are objected to because the content thereof is not in accordance with 37 CFR 1.98(a), which recites:

37 CFR§ 1.83 Content of drawing.

(a) The drawing in a nonprovisional application must show every feature of the invention specified in the claims. However, conventional features disclosed in the description and claims, where their detailed illustration is not essential for a proper understanding of the invention, should be illustrated in the drawing in the form of a graphical drawing symbol or a labeled representation (e.g., a labeled rectangular box). In addition, tables and sequence listings that are included in the specification are, except for applications filed under 35 U.S.C. 371, not permitted to be included in the drawings.

4. In the instant case the sequences that are included in the sequence listing are also included in the figures, as stated above, *tables and sequence listings that are included in the specification are, except for applications filed under 35 U.S.C. 371, not permitted to be included in the drawings*.

5. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet,

and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Response to Arguments

Claim Rejections - 35 USC § 112

6. Claims 1-3, and 5 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the prior Office Action. (Written Description).

7. Applicant's arguments filed 10-31-05 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the amendment to claim 1 to recite that the claimed antisense oligonucleotide hybridizes under physiological conditions through Watson-Crick or Hoogsteen base pairing to one or more (but not all) HDAC sequence selected from the group consisting of HDAC-1,

HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8 renders it adequately described in the specification and overcomes these two elements of the written description rejection. Furthermore, Applicants argue that the amendment to claim 1 to recite "from about 15 to about 26 nucleotides" overcomes the presently maintained written description rejection.

8. Contrary to Applicant's assertions, the breadth of the claimed invention encompasses those oligonucleotides which possess a specific function, namely those that inhibit one or more specific histone deacetylase isoforms selected from the group consisting of HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8, but less than all histone deacetylase isoforms, wherein said histone deacetylase isoforms include those selected from all species which encode this enzyme, as well as all allelic and polymorphic variants of these enzymes. It is noted that the specification as filed includes only antisense compounds that hybridize to the Human form of these enzymes (see Table 1). However, the claims are not limited to the Human-Isotype specific antisense oligonucleotides as exemplified in the specification as filed. Moreover, Applicants are not in possession of the full scope of antisense oligonucleotides encompassed by the instant claims, which read on antisense oligonucleotides that hybridizes under physiological conditions to *a region* of RNA or double-stranded DNA that encodes a *portion* of HDAC-1 (SEQ ID NO: 2). In other words, the scope of the antisense compounds of the present invention includes those that hybridize to DNA or RNA *of undefined length* that "comprises" a region of *undefined length* of the sequence set forth in SEQ ID NO: 2.

However, apart from the antisense oligonucleotides targeting human HDAC isoforms of HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8, as set forth in Table 1 (including SEQ ID NO: 17-33), specification as filed does not provide a clear nexus between the full scope of antisense oligonucleotides recited in the claims, specifically those antisense compounds targeting non-human forms of HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8, and the specifically defined function recited in these claims. The structures of the antisense oligonucleotides described in the specification as filed, cannot be used to predict the full scope of antisense oligonucleotides encompassed by the instant claims. For example, the mismatch control oligonucleotide HDAC-1 MM effectively inhibits the expression of HDAC-2, HDAC-3, and HDAC-4, however HDAC-1 was not very effective against HDAC-1. The mismatch control is complementary (i.e. hydrogen bonds via Watson Crick base pairing) to nucleotides 1594-1598 of HDAC-1 SEQ ID NO: 2, and functions to inhibit one or more specific histone deacetylase isoforms, but less than all histone deacetylase isoforms. The observation that even the mismatch control oligonucleotide HDAC-1 MM meets all the limitations of the instant claims provides further evidence that the breadth of the claimed invention is extremely broad.

Moreover, the specification as filed describes the sequences of *human* HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8, and provides methods for determining the ability of a putative oligonucleotide to inhibit one or more specific histone deacetylase isoforms, but less than all of the histone deacetylase isoforms according to HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-

7, and HDAC-8. However, a generic search of term "histone deacetylase," in GenBank resulted in 263 hits for genes encoding a histone deacetylase. This search demonstrates that there is an extremely large number of nucleic acid sequences encoding histone deacetylase isoforms, that were not adequately described in the specification as filed. Therefore, it is unclear how Applicants were in possession of the full scope of oligonucleotides which function to inhibit one or more specific deacetylase isoforms, but less than all of the histone deacetylase isoforms, when all of the isoforms of histone deacetylase were not know as of the earliest effective filing date of the current application. (See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement.; and MPEP § 2163).

As stated in the prior Office Action, Branch (1998) states that "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found ***empirically*** by screening a large number of candidates for their ability to act inside cells." (page 49, col. 1, paragraph 3)

Although Applicants provide a means for testing the ability of a putative oligonucleotide to inhibit one or more deacetylase isoforms according to *human* HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8, there is no guidance provided in the specification as filed or in the prior art searched that would have allowed the skilled artisan to predict the structures oligonucleotides according to the present invention that inhibit the expression of one or more non-human HDAC isoforms of HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and

HDAC-8, but not all of the *non-human* isoforms of the histone deacetylase genes recited in the instant claims. Apart from further experimentation, the skilled artisan would not have been able to predict the structures of the full scope of the claimed oligonucleotides encompassed by the instant invention. According to MPEP § 2163, providing a method for isolating the claimed invention is not evidence of description.

9. The rejection of claims 1-3 and 5 under 35 U.S.C. 112, first paragraph, for lack of enablement is withdrawn in response to Applicant's amendment.

Claim Rejections - 35 USC § 103

10. The rejection of claims 1-3 and 5 under 35 U.S.C. 103(a) as set forth in the prior Office Action is withdrawn in response to Applicant's arguments and amendments.

11. The rejection of claims 1 under 35 U.S.C. 102(b) is withdrawn as being anticipated by Schreiber et al. (WO 97/35990 A2), in response to Applicant's arguments.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting

directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 1-3, and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Besterman et al. (US Patent No. 6,953,783.)

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Besterman et al. discloses antisense oligonucleotides having the sequences according SEQ ID NO: 43-44. SEQ ID NO: 43 of Besterman et al. is identical to SEQ ID NO: 18 of the instant application. SEQ ID NO: 44 is identical SEQ ID NO: 17 of the instant application. Besterman et al. also teaches that the disclosed oligonucleotides preferably comprise phosphorothioate modifications, and an hybrid or chimeric structure.

> For purposes of the invention, a "chimeric oligonucleotide" refers to an oligonucleotide having more than one type of internucleoside linkage. One preferred example of such a chimeric oligonucleotide is a chimeric oligonucleotide comprising a phosphorothioate, phosphodiester or phosphorodithioate region, preferably comprising from about 2 to about 12 nucleotides, and an alkylphosphonate or alkylphosphonothioate region (see e.g., Pederson et al. U.S. Pat. Nos. 5,635,377 and 5,366,878). Preferably, such chimeric oligonucleotides contain at least three consecutive internucleoside linkages selected from phosphodiester and phosphorothioate linkages, or combinations thereof.
>
> For purposes of the invention, a "hybrid oligonucleotide" refers to an oligonucleotide having more than one type of nucleoside. One preferred example of such a hybrid oligonucleotide comprises a ribonucleotide or 2'-O-substituted ribonucleotide region, preferably comprising from about 2 to about 12 2'-O-substituted nucleotides, and a deoxyribonucleotide region. Preferably, such a hybrid oligonucleotide will contain at least three consecutive deoxyribonucleosides and will also contain ribonucleosides, 2'-O-substituted ribonucleosides, or combinations thereof (see e.g., Metelev and Agrawal, U.S. Pat. No. 5,652,355).

(See for col. 12, lines 20-43).

Besterman et al. teach each and every aspect of the instant claims, thereby anticipating the claimed invention.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-3, 5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Besterman et al. as applied to claims 1-3 and 7 above, in view of Bennett et al. (1996, see PTO-892 mailed 8/06/2002, Reference "U").

Besterman et al. teach each aspect of instant claims 1-3 and 7. As stated above, the teachings of Besterman et al. comprises wherein the disclosed oligonucleotides are hybrid oligonucleotides, containing at least three consecutive deoxyribonucleotides, and 2'-O-substituted ribonucleosides. However, Besterman et al. do not disclose the oligonucleotide compounds of the instant invention wherein said oligonucleotide:

> 5. (Previously presented) The oligonucleotide according to claim 1, being 20-26 nucleotides in length and being modified such that the terminal four nucleotides at the 5' end of the oligonucleotide and the terminal four nucleotides at the 3' end of the oligonucleotide each have 2'-O-methyl groups attached to their sugar residues.

According to Bennett et al. (1996; antisense compounds designed wherein the terminal nucleotides comprise 2'-O-methyl modifications, and further comprising an internal unmodified region, have increased nuclease stability, increased potency, and enhanced pharmacokinetic properties, in comparison with unmodified antisense compounds (see page 38, 1st paragraph).

It would have been obvious to the ordinary skilled artisan at the time of the instant invention, to modify the antisense compounds of Besterman et al. to comprise the modification as recited in the instant claimed. Absent evidence to the contrary, the ordinary skilled artisan would have been motivated to make the claimed modified oligonucleotides since the prior art teaches that these modifications are known to enhance the properties of these compounds in a cellular environment, for example increase nuclease stability as described above.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1-3, 5 and 7 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 10/870,587. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the claims of the instant

application and those of the copending application are drawn to agents that inhibit one or more specific histone deacetylase isoforms but less than all histone deacetylase isoforms, the scope of the instant claims are drawn to one or more oligonucleotides that function to inhibit one or more specific HDAC isoforms. The limitation wherein the agent is an oligonucleotide as recited in the instant claims is clear disclosed in copending claims 2-11. Moreover, the specific modifications describe in instant claims 2-3 and 5 are clearly described in copending claims 4-5, and 9. Additionally, the specific sequences recited in claim 7, namely SEQ ID NO: 17-18 is expressly recited in copending claim 11. Each and every aspect of the instant claims is anticipated by or obvious over one or more aspects of the claims of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 9:30 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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